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THE HUMAN GENOME: FUTURE DIRECTIONS AND BOOK REVIEWS

FUTURE DIRECTIONS: GENOMICS AND SOCIETY

The Human Genome and Our View of Ourselves

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Perhaps for the pragmatic biologist, the determination of the human genome sequence is a prosaic event—the delivery of a wonderfully powerful tool, but a tool nonetheless. For the general public, however, the human genome sequence is of enormous symbolic significance, and its publication on page 1304 of this issue (*1*) and in this week's *Nature* (*2*) is likely to be greeted with the same awestruck feeling that accompanied the landing of the first human on the moon and the detonation of the first atomic bomb.

Why are certain achievements—the first lunar landing, atomic fission, the determination of the human genome sequence—imbued with such emblematic significance? The reason is, I believe, that they change how we think about ourselves. Landing a person on the moon gave us an extraterrestrial perspective on human life; atomic fission gave us the power to create enormous energy reserves and to extinguish all human life on Earth; and now the human genome sequence gives us a view of the internal genetic scaffold around which every human life is molded. This scaffold has been handed down to us from our ancestors, and through it we are connected to all other life on Earth.

How does the complete human genome sequence affect the way that we think about ourselves? Clearly, the availability of a reference human DNA sequence is a milestone toward understanding how humans have evolved, because it opens the door to large-scale comparative studies. The major impact of such studies will be to reveal just how similar humans are to each other and to other species.

The first comparisons will be between the human genome and distantly related genomes such as those of yeast, flies, worms, and mice. A glimpse of what this will show us comes from considering the fact that about 26,000 to 38,000 genes are found in the draft version of our own genome, a number that is only two to three times larger than the 13,600 genes in the fruit fly genome. Furthermore, some 10% of human genes are clearly related to particular genes in the fly and the worm. So, obviously, we share much of our genetic scaffold even with very distant relatives. The similarity between humans and other animals will become even more evident when genome sequences from organisms such as the mouse, with whom we share a more recent common ancestor, become available. For these species, both the number of genes and the general structure of the genome are likely to be very similar to ours. Although this has long been realized by insiders in the genetics community, the close similarity of our genome to those of other organisms will make the unity of life more obvious to everyone. No doubt the genomic view of our place in nature will be both a source of humility and a blow to the idea of human uniqueness.

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However, the most obvious challenge to the notion of human uniqueness is likely to come from comparisons of genomes of closely related species. We already know that the overall DNA sequence similarity between humans and chimpanzees is about 99% (*3*). When the chimpanzee genome sequence becomes available, we are sure to find that its gene content and organization are very similar (if not identical) to our own. Perhaps it is our subconscious discomfort with this expectation that explains the slowness with which the genomics community has embraced the idea of a chimpanzee genome project. Be that as it may, with most of the human genome sequence now complete, it will be easy to determine the chimpanzee sequence using the human sequence as a guide to assembly. The result is sure to be an even more powerful challenge to the notion of human uniqueness than the comparison of the human genome to those of other mammals.

Yet the few differences between our genome and those of the great apes will be profoundly interesting because among them lie the genetic prerequisites that make us different from all other animals. In particular, these differences may reveal the genetic foundation for our rapid cultural evolution and geographic expansion, which started between 150,000 and 50,000 years ago (*4*) and led to our current overbearing domination of Earth. The realization that one or a few genetic accidents made human history possible will provide us with a whole new set of philosophical challenges to think about.

Large-scale comparisons of human genomes from many individuals are now possible with the emergence of high-throughput techniques for DNA sequence determination. The general picture already apparent from such studies is that the gene pool in Africa contains more variation than elsewhere, and that the genetic variation found outside of Africa represents only a subset of that found within the African continent (*5*). From a genetic perspective, all humans are therefore Africans, either residing in Africa or in recent exile.

In view of the sad part that race and ethnicity still play in most societies, concerns that genetic analyses of different human populations could be abused are appropriate. Fortunately, from the few studies of nu-

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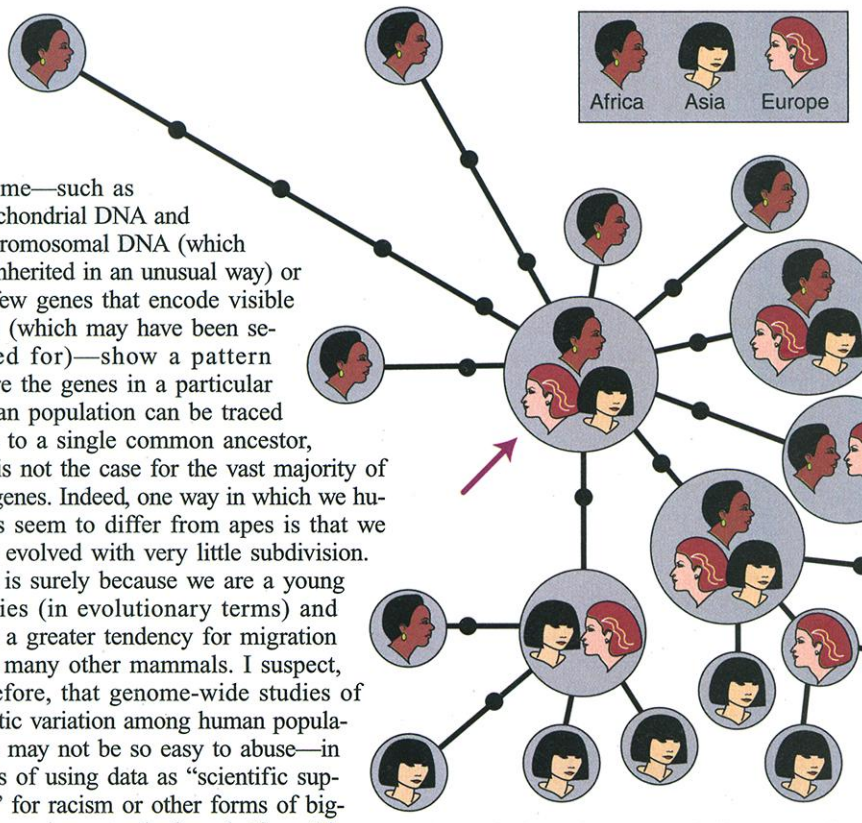
clear DNA sequences, it is clear that what is called "race," although culturally important, reflects just a few continuous traits determined by a tiny fraction of our genes. This tiny fraction gives no indication of variations at other parts of our genome. Thus, from the perspective of nuclear genes, it is often the case that two persons from the same part of the world who look superficially alike are less related to each other than they are to persons from other parts of the world who may look very different (see the figure) (*6*). Although small segments of the genome—such as mitochondrial DNA and Y chromosomal DNA (which are inherited in an unusual way) or the few genes that encode visible traits (which may have been selected for)—show a pattern where the genes in a particular human population can be traced back to a single common ancestor, this is not the case for the vast majority of our genes. Indeed, one way in which we humans seem to differ from apes is that we have evolved with very little subdivision. This is surely because we are a young species (in evolutionary terms) and have a greater tendency for migration than many other mammals. I suspect, therefore, that genome-wide studies of genetic variation among human populations may not be so easy to abuse—in terms of using data as "scientific support" for racism or other forms of bigotry—as is currently feared. If anything, such studies will have the opposite effect because prejudice, oppression, and racism feed on ignorance. Knowledge of the genome should foster compassion, not only because our gene pool is extremely mixed, but also because a more comprehensive understanding of how our genotype relates to our phenotype will demonstrate that everyone carries at least some deleterious alleles. Consequently, stigmatizing any particular group of individuals on the basis of ethnicity or carrier status for certain alleles will be revealed as absurd.

From a medical standpoint, improved predictive capabilities provided by the identification of disease-associated alleles harbor great potential benefits but also problems. The benefits will come from using individualized risk assessment to modify the environmental and behavioral components of common diseases. Relatively minor measures implemented early in life may prove to be extremely effective in postponing or even preventing the onset of disease. But individualized risk assessment may come at the price of "genetic hypochondria," causing many to spend their lives waiting for a disease that may never arrive. Finally, increased medical predictive power obviously represents a societal challenge in terms of medical insurance, especially in countries that, unlike most Western European countries, are not blessed with health insurance systems that share risks in an equitable fashion among the whole population. Legislators in such countries would be wise to act now to counteract future temptations to "personalize" insurance risks. Later on, once powerful genetic diagnostic tests are in place, it will be hard to withstand pressure from the insurance lobby to prevent such legislation.



The global family. A network illustrating the relatedness of a series of DNA sequences within a 10,000–base pair segment of the human X chromosome sampled from 70 individuals worldwide. Identical DNA sequences found in people living on three different continents are illustrated by circles containing three faces; identical DNA sequences found in individuals from two continents are depicted as circles containing two faces; sequences that are found only among individuals inhabiting one continent are depicted as circles containing one face. A DNA sequence that is ancestral to all of the other sequences (arrow) is found in individuals from all continents. Black dots on the lines connecting the circles denote nucleotide substitutions in the DNA sequences. The network demonstrates that people from different continents often carry identical DNA sequences. Consequently, how a person looks gives little or no clue to what alleles he or she may carry at any particular locus. [Modified from (*6*)]

As we enter a genomic era in medicine and biology, perhaps the greatest danger I see stems from the enormous emphasis placed on the human genome by the media. The successes of medical genetics and genomics during the last decade have resulted in a sharp shift toward an almost completely genetic view of ourselves. I find it striking that 10 years ago, a geneticist had to defend the idea that not only the environment but also genes shape human development. Today, one feels compelled to stress that there is a large environmental component to common diseases, behavior, and personality traits! There is an insidious tendency to look to our genes for most aspects of our "humanness," and to forget that the genome is but an internal scaffold for our existence.

We need to leave behind the view that the genetic history of our species is *the* history par excellence. We must realize that our genes are but one aspect of our history, and that there are many other histories that are even more important. For example, many people in the Western world feel a connection to ancient Greece, from which arose fundamental features of Western architecture, science, technology, and political ideals (such as democracy). Yet, at best a tiny fraction of the gene pool of the Western industrialized world came from the ancient Greeks. Obviously, this fact in no way diminishes the importance of ancient Greece. So it is a delusion to think that genomics in isolation will ever tell us what it means to be human. To work toward that lofty goal, we need an approach that includes the cognitive sciences, primatology, the social sciences, and the humanities. But with the availability of the complete human genome sequence now at hand, genetics is in a prime position to play a prominent part in this endeavor.

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